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Spectral Analysis of Lithium Tremor

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ABSTRACT

Introduction: Lithium has proven efficacy in bipolar affective disorder (BAD) but induces tremor as a side effect in a quarter of patients. Lithium tremor (LT) shares some clinical characteristics of essential tremor (ET) and Parkinson's disease tremor (PT), which might cause difficulties in differential diagnosis. Furthermore, current knowledge of LT is lacking detailed electrophysiological characterization. Here, we present detailed spectral attributes of accelerometric tremor recordings as a diagnostic tool for LT.

Methods: 10 patients (7 males, 3 females) between ages of 29–68, who were on lithium for BAD for 2–12 years, were evaluated for hand tremor with the spectral analysis of accelerometric recordings with different postures. Tremor severity was rated clinically on WHIGET (Washington Heights-Inwood Genetic Study of Essential Tremor) scale. Results were analyzed in comparison to results of ET (n=19) and PT (n=19) patients from our database.

Results: LT was most prominent at extensor postures with an average peak frequency (PF) of 8.0±0.3 Hz and an extremely low amplitude, high harmonic components and high noise level. The average PF of LT was similar to that of ET (7.3±0.4 Hz), but higher than that of PT (5.3±0.2 Hz) (p<0.0001). With weight loading, the PF of LT showed an increase of 1.3 Hz. Average amplitude of PT was higher than that of both LT and ET (p<0.0001); harmonic components of LT was comparable to PT whereas noise levels were similar to that of ET. Mean WHIGET score of LT (6.5±0.5) was significantly lower than that of ET (13.1±1) (p<0.0001).

Conclusion: Electrophysiological features detected by accelerometry may help in differential diagnosis of LT from ET and PT.

Keywords: Lithium tremor, accelerometry, tremorogram, peak frequency, harmonic components

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INTRODUCTION

Lithium is a common drug of choice in the treatment of bipolar affective disorder (BAD) and is also on the top of the list of tremorogenic drugs (1, 2). In 1959, Schou described this common side effect of lithium, as a fine postural tremor which may be detected even at very low doses of treatment (3). In 1986, Hallett classified it as a postural tremor with a peak frequency of 8–12 Hz, closely resembling exaggerated physiological tremor (4). It is more frequently encountered at the beginning of treatment and tends to disappear during chronic treatment. Usually, there is no correlation between serum lithium levels and tremor (5, 6). It may also evolve to a different kind of tremor resembling parkinsonian type in time (7). Aging, previous history of tremor and concomitant use of other tremorogenic medications like valproic acid, tricyclic anti-depressants, or serotonin reuptake inhibitors increase the risk of lithium tremor (LT) (5, 8, 9).

Tremor is encountered in 27% of patients using lithium, this percentage varies between 4 to 65 depending on the study (9). This frequent side effect is an important cause of drug non-compliance; in one study 32% of the patients reported that the tremor was one of the most disturbing side effects leading to non-compliance (10). Moreover, lithium may induce other parkinsonian features such as bradykinesia and rigidity (11). For confirming the diagnosis of LT, there should be either a temporal relationship between tremor and initiation of lithium treatment, or tremor should disappear after discontinuation of lithium (9).

It is necessary to make a differential diagnosis for essential tremor (ET) and Parkinson's disease with tremor (PT) especially when the patient is older, experiencing some slowness in movements as well, or has a family history of tremor. Myoclonus is another side effect of chronic lithium treatment and it is mostly cortical in origin, clinically more rhythmic in appearance, and resembling tremor (12, 13). Electrophysiologic evaluation is critical to rule out myoclonus in the wok-up of LT. It is also relevant to rule out tremor related to acute toxicity. At that point, accelerometric tremor analysis might be a relevant method to help clinicians to reach a more precise diagnosis. However, current knowledge of LT is lacking detailed electrophysiological characterization and clinical guidelines. Thus, in this study, we aim to delineate the characteristic electrophysiological features of LT in comparison to other common tremor disorders, to help differential diagnosis in challenging cases, to understand the underlying pathophysiology of tremor in general, and even to find more effective treatment strategies.

METHODS

Patients

Ten patients (7 males, 3 females) between ages of 29–68, who had been treated with lithium for BAD for 2–12 years at the Outpatient Clinic of the Department of Psychiatry in Hacettepe University Hospital were included

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in the study. All of the patients were on lithium monotherapy except for one receiving risperidone 2 mg/day additionally. Thyroid function tests were normal for all.

The clinical evaluations for hand tremor were performed at the Department of Neurology. WHIGET (Washington Heights-Inwood Genetic Study of Essential Tremor) Tremor Rating Scale was used for clinical rating of tremor severity, as LT is basically a postural tremor similar to ET (14, 15). This scale evaluates postural tremor when patient stretches out hands, and kinetic tremor while the patient is performing different tasks like pouring water between two cups, drinking water from a cup, drawing spirals, finger to nose movements, and using a spoon to drink water. Each task is rated between 0–3 and for each hand separately, the maximum total score is 36. All of the patients gave written informed consent.

19 patients with ET and 19 patients with PT, who were randomly chosen from an archive of previously studied patients at the EMG laboratory, were also included in the study.

Electrophysiological Analysis

Two miniature accelerometers (EGAXT-F-10, Entran Devices, Inc., Fairfield, NJ, USA), fixed in a position perpendicular to each other, formed a double-axes accelerometer which was used in all recordings. A custom-developed recording system and software were used for recordings and analyses. The signals were amplified, band-pass filtered (0.5–100 Hz), digitized (1024 Hz), and stored for later analyses.

Experiments were performed at the EMG laboratory of the Department of Neurology. Recordings were performed while patients sat upright in an armchair. The accelerometer was mounted onto the tip of the index finger in such a position that accelerations on flexion-extension and abduction-adduction axes were sensed by one of the two axes of the accelerometer. In patients with asymmetric tremor, the arm with more pronounced tremor was chosen. Otherwise, recordings were taken from the right-hand side. The recordings were made under five different positional conditions; P1: shoulder flexion, elbow and wrist extension with palms facing down and fingers splayed; P2: shoulder abduction, elbow flexion, wrist extension; P3: similar to P1 with 1 kg load suspended at the wrist; P4: arms put on the armrest of the chair, the hand dropped loose at the edge of the armrest and relaxed; and finally, P5: similar to P4 while patient subtracting serial sevens from 100. For each of the positions, a two-minutes recording was obtained.

Power Spectral Analyses

Each patient's accelerometric signals were segmented into four-second epochs. For every epoch, linear trends were removed and a Hanning window was applied before computing the power spectra using the fast Fourier method. The obtained power spectra were then ensemble-averaged. From the averaged power spectra, four variables were calculated for both accelerometric axes, for each positional condition, and for each of the patients: main (peak) tremor frequency (the frequency of the highest peak of the spectrum) (PF), power (amplitude) at this frequency, the normalized total power of the first 10 harmonic components of the peak frequency (HC), and the normalized total power of the remaining spectrum (broad-band spectral activity without a peak frequency, i. e, the "noise").

The calculated values of two accelerometric axes were summarized by averaging. To further summarize the data, the values of postural conditions (P1 and P2), and the values of resting conditions (P4 and P5) were also averaged to obtain a single postural and a single resting measure. P3 recordings (loading condition) were analyzed separately.

Statistical Analysis

Quantitative data were presented by mean ± standard error. Frequencies and percentages were given for nominal data. Quantitative data of the three patient groups were compared by Kruskal-Wallis test, and Mann-Whitney U test was conducted for post-hoc pairwise comparisons. Chi-square test was used for comparison of categorical data. Statistical significance was set at $p<0.05$. Bonferroni correction was applied for multiple comparisons.

To obtain a normal statistical distribution, a logarithmic transformation was applied to the amplitude data. To avoid statistical artifacts arising from very low amplitude values (recordings with absent or very low amplitude tremors), the transformed amplitudes were also categorized into three groups as low, intermediate, and high amplitudes; and processed accordingly as categorical data.

RESULTS

Age, gender, duration of treatment in years, lithium dose (mg/day), serum lithium level (mmol/L) on the day of accelerometry and WHIGET scores of the patients are given in Table 1. Serum lithium levels were in the therapeutic window for all of the patients except for one very slightly above the range. The mean score from WHIGET severity scale was 6.5±0.5 for the patients with LT. This was significantly lower than the mean score of ET patients (13.1±1.0, $p<0.0001$). Only one LT patient had a family history of ET. Mean age of the patients and female/male ratios were similar between LT, ET, and PT groups (Table 2).

Table 1. Demographic and clinical features of the patients included in the study

Patient number	Age	Gender	Duration of treatment (years)	Lithium dose (mg/day)	Serum lithium level (mmol/L) N: 0.6-1	WHIGET score
1	29	F	12	1500	0.94	10
2	29	M	2	1200	0.71	5
3	40	M	3	1200	0.74	6
4	53	M	6	1500/1800 alternatively	0.92	6
5	68	F	10	600	0.38	5
6	51	M	7	1800	0.97	6
7	31	F	10	1500	0.61	7
8	55	M	2	1800	0.86	7
9	50	M	21	2400	0.9	8
10	62	M	10	900	1.24	5
Mean±SEM	46.8±4.4	3/7 (F/M)	8.3±1.8	1455±161	0.83±0.07	6.5±0.5

Table 2. Detailed electrophysiological properties of LT, ET and PT determined by spectral analysis

	LT (N= 10) Mean±SEM	ET (N= 19) Mean±SEM	PT (N= 19) Mean±SEM	p Kruskal-Wallis	p LT vs ET	p LT vs PT	p ET vs PT
Age	46.8±4.4	49.7±3.8	59±2.8	0.08			
Gender (F/M)	3/7	11/8	5/14	0.11[ae]			
Average PF	8.0±0.3	7.3±0.4	5.3±0.2	**<0.0001***	0.06	**<0.0001***	**<0.0001***
PF at extensor posture (Hz)	7.7±0.5	7.2±0.4	5.4±0.2	**<0.0001***	0.1	**<0.0001***	**<0.0001***
PF with loading (Hz)	9.0±0.2	7.6±0.5	5.9±0.3	**<0.0001***	**0.009***	**<0.0001***	**0.006***
PF at rest (Hz)	7.4±0.5	7.1±0.5	4.9±0.2	**<0.0001***	0.5	**<0.0001***	**<0.0001***
Average amp	-0.8±0.2	0.5±0.4	2.6±0.4	**<0.0001***	0.03	**<0.0001***	**<0.0001***
Amp at extensor posture	-0.7±0.2	0.9±0.4	2.7±0.4	**<0.0001***	**<0.0001***	**<0.0001***	**0.008***
Amp with loading	-0.3±0.3	0.8±0.3	2.2±0.5	**0.005***	0.04	**0.003***	0.06
Amp at rest	-1.9±0.4	-0.2±0.5	3.2±0.3	**<0.0001***	0.03	**<0.0001***	**<0.0001***
Average HC	38.22±4.4	24.0±2.1	40.0±3.5	**0.001***	**0.006***	0.7	**<0.0001***
HC at extensor posture	46.4±5.9	24.7±2.3	41.5±4.5	**0.001***	**0.001***	0.4	**0.002***
HC with loading	21.9±2.4	22.5±2.5	40.5±5.3	**0.01***	0.8	**0.002***	**0.003***
HC at rest	77.3±6	31.5±2.6	41.4±2.9	**<0.0001***	**<0.0001***	**<0.0001***	0.04
Average noise	518.6±44.7	270±27.8	243.5±26.2	**<0.0001***	**<0.0001***	**<0.0001***	0.5
Noise at extensor posture	552.6±48.2	260.9±28.8	240.2±26.3	**<0.0001***	**<0.0001***	**<0.0001***	0.6
Noise with loading	450.7±47.6	288.3±33.6	269.8±33.6	**0.002***	**0.008**	**0.004***	0.6
Noise at rest	604.8±100.4	361.2±46.8	165.9±18	**<0.0001***	0.04	**<0.0001***	**<0.0001***

For post-hoc pairwise comparisons p value is 0.017 after Bonferroni correction.
amp, amplitude; ET, essential tremor; f, female; HC, harmonic component; Hz, hertz; LT, lithium tremor; m, male; PF, peak frequency; PT, Parkinson's disease tremor; SEM, standard error of mean; [ae]Pearson Chi-square p value.

Table 3. Comparison of amplitudes between groups after classifying as low, intermediate and high

		LT (N= 10) % (n)	ET (N= 19) % (n)	PT (N= 19) % (n)
Average amp	Low	30 (3)	10.5 (2)	-
	Intermediate	70 (7)	73.7 (14)	**26.3 (5)**
	High	-	15.8 (3)	**73.7 (14)**
Amp at extensor posture	Low	40 (4)	5.3 (1)	10.5 (2)
	Intermediate	60 (6)	**78.9 (15)**	**15.8 (3)**
	High	-	15.8 (3)	**73.7 (14)**
Amp with loading	Low	20 (2)	5.3 (1)	-
	Intermediate	80 (8)	78.9 (15)	44.4 (8)
	High	-	15.8 (3)	**55.6 (10)**
Amp at rest	Low	**80 (4)**	31.6 (6)	-
	Intermediate	20 (1)	52.6 (10)	15.8 (3)
	High	-	**15.8 (3)**	**84.2 (16)**

Post-hoc pairwise comparisons showed significant association between intermediate (p=0.002) and high average amplitudes (p=0.00001) and PT; at extensor postures intermediate amplitude and ET (p=0.002) and intermediate (p=0.0001) and high amplitudes (p=0.00001) and PT showed significant association. With weight loading, only significant association was between high amplitudes and PT (p=0.0007). At rest the association between low amplitudes and LT (p=0.002), high amplitudes and ET (p=0.001) and both low (p=0.002) and high amplitudes (p<0.00001) and PT was detected. These significant associations are marked as bold in the table.
For post-hoc pairwise comparisons p value is 0.0055 after Bonferroni correction.
amp, amplitude.

In LT patients, a tremor activity with an extremely low amplitude (all positions), high noise level (all positions) and high HC (resting), with an overall average PF (in all positions) of 8.0±0.3 Hz, was detected (Table 2). Five out of 10 patients did not have any tremor either at rest or during performing a cognitive task at rest. The overall average PF of both LT (8.0±0.3 Hz) and ET (7.3±0.4 Hz) were significantly higher than that of PT (5.3±0.2 Hz) (Figure 1a). Similarly, the PF of postural and resting tremor were significantly higher for LT and ET compared to PT (Table 2, Figure 1a). With weight loading, the PF of postural LT showed an increase of around 1.3 Hz, while it was stable for ET and PT, and this led to a significant discrimination between PF of LT and ET (Figure 1a).

The normalized overall average amplitude (in all positions) of LT was the lowest and that of PT was the highest of three groups (Table 2, Figure 1b). While amplitude of only postural ET was higher than that of LT, the amplitude was higher in PT for all positions compared to that of LT and ET (Figure 1b). After ln (natural logarithm) conversion, the amplitude values distributed between -4 and 5, so values less than -1 were classified as low, those between -1 and 2 as intermediate and the ones more than 2 as high. The percentages of patients in each level for three tremor syndromes were given in Table 3. Details of post-hoc pairwise comparisons for proportions of patients in each category can be found in the table legend.

Harmonic components of LT were found to be as high as that of PT and both were higher than that of ET especially at extensor postures (Table 2, Figure 1c). At rest HC of LT increased even more and became higher than that of PT, and on contrary it decreased with weight loading and this time it was lower than that of PT and similar to ET (Table 2, Figure 1c). As number of LT patients with resting tremor was lower (n=5) and resting

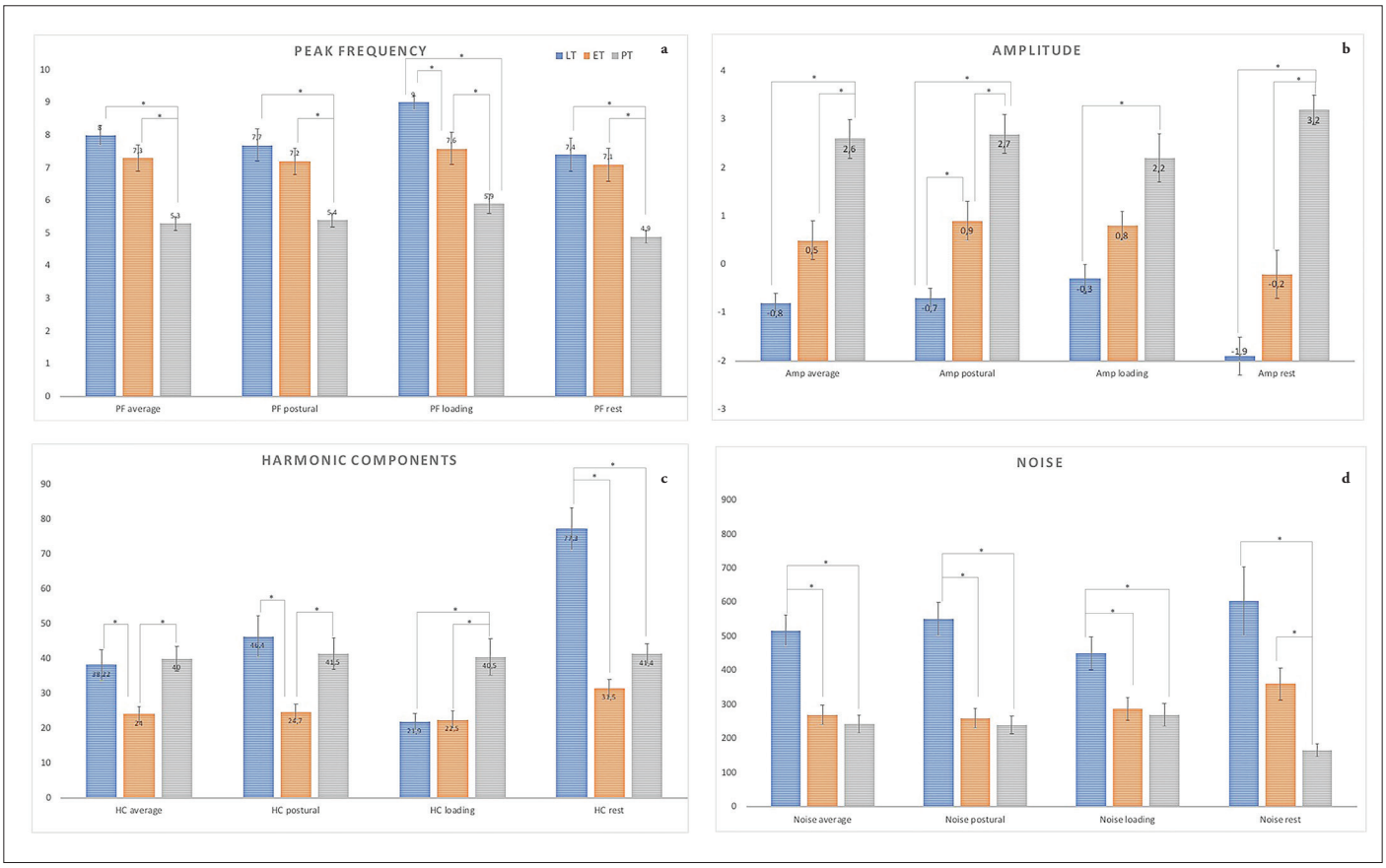

Figure 1. Comparison of peak frequency **(a)**, amplitude **(b)**, harmonic components **(c)** and noise **(d)** values on average and under different conditions (postural, loading and rest) between LT, ET and PT groups (*significant p value).

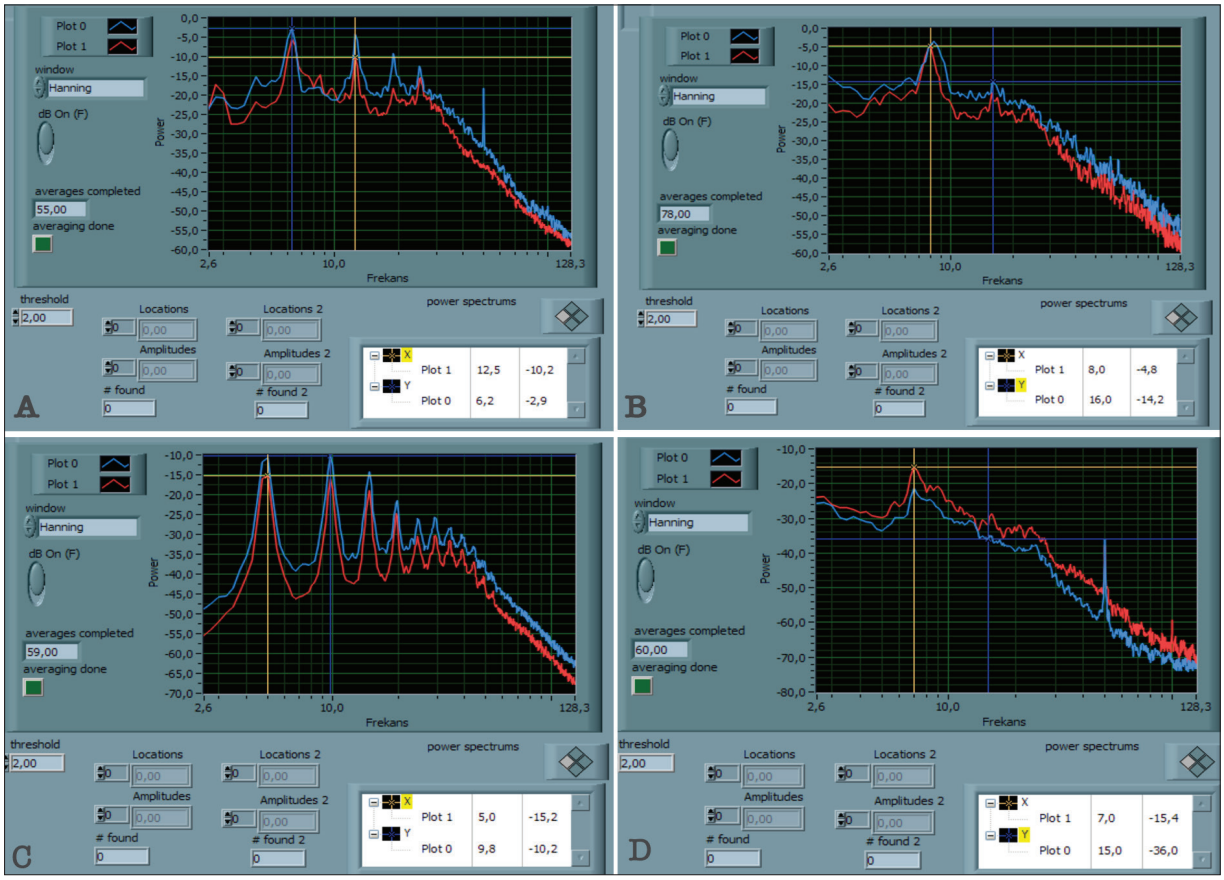

Figure 2. Representative spectral analysis of LT at rest **(a)**, at extensor posture **(b)**, Parkinsonian tremor **(c)** and essential tremor **(d)**.

tremor amplitude was extremely low, these high HC may be misleading, and therefore this finding should be disregarded. The noise ratio of LT was the highest for all positions, only at resting it was similar to that of ET (Table 2, Figure 1d).

Representative examples of spectral analysis results are presented in Figure 2. HC of LT at rest in Figure 2a look similar to those of PT at rest in Figure 2c. Noise ratio of LT is high both at rest and at extensor posture (Figure 2a, 2b), similar to ET at extensor posture (Figure 2d).

DISCUSSION

LT is a non-progressive, symmetric postural tremor limited to hands and upper limbs. It is variable in frequency and intensity, and more irregular in nature. Even though correlation between serum levels and tremor severity is lacking, it may generalize in case of toxicity, and becomes coarser and more severe. The prevalence of LT is highly variable between studies as previous tremor history may not have been recorded in most of the studies; the evaluation method (subjective/objective) may be different; patients may also be using other drugs which potentiate or suppress tremor and patients' mood at the time of evaluation may have an impact on the proportion of patients with tremor (9). In one study, the PF of tremor was found to decrease from exaggerated physiologic tremor range to parkinsonian range with chronic use (7).

In the clinical settings, LT is mostly evaluated by simple observation and brief neurologic examination. In addition, both subjective measures i. e. clinical tremor rating scales, evaluation of the writing or Archimedean spiral drawing of the patient; and objective functional performance tests i.e. drinking water from a cup, pouring water from cup to cup, nine-hole pegboard test could be used (16).

Electrophysiological characterization of common tremor syndromes like ET, PT, and exaggerated physiological tremor have been extensively dissected using different methods (17), whereas there are only a few studies investigating LT (7, 8, 18). The first one is a rather old study evaluating tremor characteristics of 23 patients who were on lithium treatment for more than 6 months (6–108 months). They found the PF as 8 Hz and showed that with chronic lithium use, it decreased from physiologic tremor range to PT range and the amount of tremor increased (7). The same group also evaluated acute LT using similar methodology and concluded that acute LT was similar to exaggerated physiologic tremor (18).

The other study published by Zaninelli et al. in 2001, was performed in patients who were on lithium prophylaxis (serum levels between 0.5 to 0.8 mmol/L) and had a major depressive episode, so either paroxetine 20 mg/day (n=14) or amitriptyline 75 mg/day (n=17) was added to their treatment as an antidepressant (8). The authors tested the hypothesis that, with an increase of serotonergic activity, tremor severity may increase and change characteristics. By comparing the area under curve in power spectral analysis, they found that the PF did not change throughout the study and was similar between groups (paroxetine group, 7.4±2.3 Hz, range 5–12 Hz; amitriptyline group, 7.5±1 Hz, range 6–9 Hz) (8).

According to our findings, LT is clinically a mild postural tremor with a low overall average amplitude and has a PF of 8.0 Hz, which increases with weight loading. Its HC is comparable to PT and noise levels are highly similar to ET. Thus, LT could be distinguished from ET by increase in PF with weight loading and high HC. LT could also be differentiated from PT by its lower amplitude, higher PF, and noise level.

Decrease in PF with weight loading more than 1 Hz points is a common feature of exaggerated physiologic tremor (17, 19). On the other hand, an increase in the PF after weighting, as was the case with LT in our study, usually observed in functional tremor, while it may also be encountered in ET and PT (20). As this was shown for the first time, we believe that our finding of increase in PF with weight loading in LT needs to be approved in further electrophysiological studies.

The functional significance of harmonic activity is controversial. High harmonic activity is usually associated with PT, but it is not clear if twofold PF is whether the second harmonic or a physiological tremor peak at around 12 Hz or a mechanoreceptor feedback activity (21). In our study, HC of LT in extensor positions (excluding weight loading) was significantly higher than that of ET. This finding might be an important discriminating feature and may shed light on the pathophysiology of LT. As previously mentioned in the results section, since the number of LT patients with resting tremor was not enough and resting tremor amplitude was extremely low, high HC in LT with resting positions were disregarded.

This study has several limitations. First of all, the number of LT patients is low. A higher number of patients may provide better information about general electrophysiological features of LT. Second, there is high interindividual variability in the number of years under lithium therapy. Third, as Parkinsonian signs due to lithium treatment were not rated in patients, possible additional effect on tremor could not be distinguished. Lastly, as mean tremor severity was low for LT; more severe cases might have been included to look for the variability in electrophysiologic parameters.

Electrophysiological evaluation may provide invaluable diagnostic information on the top of clinical examination of a patient with the complaint of tremor. Accelerometric characterization of a tremor may also help to clarify the underlying pathophysiological factors. It is a practical, low-cost, and quick way of analyzing tremor. Further electrophysiological studies of LT and other drug-induced tremors are needed. To our knowledge, our study is the first one in the literature describing electrophysiological features of LT in comparison to ET and PT. These parameters may aid in the differential diagnosis of difficult cases.

In conclusion, our results show that it is possible to differentiate LT from other tremor disorders with similar clinical and electrophysiological features such as ET and PT by using spectral analysis of accelerometric tremor recordings.

Ethics Committee Approval: The study was approved by Hacettepe University Non-interventional Clinical Researches Ethics Board (decision number: GO 20/426).

Informed Consent: All of the patients gave written informed consent.

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